9. (Amended) A method for transplanting cells to a patient in need thereof, comprising:

a) obtaining cells from a donor,

b) obtaining a tissue, an organ, or recipient cells from the patient,

c) contacting the donor cells with an immunoglobulin specific to B7-1, an immunoglobulin specific to B7-2, and the tissue, the organ, or the recipient cells that express MHC Class I antigen, B7-1 and B7-2 molecules, for a period of time from about 1 to about 48 hours, thereby obtaining a mixture, and

d) introducing the mixture to the patient.

REMARKS

I. The Specification

Corrected drawings in compliance with 37 CFR § 1.85 are submitted herewith.

The specification is amended herein to merely correct a typographical error; the term "I2R" has been replaced with "III2R". Support for this correction can be found at least at page 35 of the specification which indicates that human heavy chain framework sequences that were used to humanize the 3D1 antibody were from the human subgroup I (see e.g., page 35, lines 13-17). Page 35 of the specification also states that the heavy chain framework sequences were published by Manheimer-Lory, A. *et al.*, J. Exp. Med. 174(6):1639-1652 (1991) (a copy is enclosed with the concurrently filed Information Disclosure Statement). Table I of the Manheimer-Lory reference teaches only two cell lines with the heavy chain variable regions belonging to subtype I: the III2R cell line and the R3.5H5G cell line. It is clear that the use of the term "I2R" rather than

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"III2R" throughout the specification was a typographical error. Accordingly, the term "I2R" has been replaced with "III2R" at each occurrence. No new matter has been added.

The Examiner has required that the application be reviewed for all spelling, trademarks, and like errors to be corrected. Applicants have made every effort to detect and correct such errors in the specification. Applicants submit that the trademarks known to Applicants are capitalized, and that the proprietary nature of the marks has been respected.

II. Status of the Claims

Claims 1-10 are currently pending. Claims 1 and 9 have been amended to more particularly point out and distinctly claim the subject matter Applicants regard as their invention. Support for these amendments and new claims can be found throughout the specification and claims as originally filed. Support for the limitation "from about 1 to about 48 hours" can be found on page 7, lines 5-6. No new matter has been added.

III. The Rejection Under 35 U.S.C. § 102(e)

Claims 1-4 stand rejected under 35 U.S.C. § 102(e) as allegedly anticipated by Freeman *et al.* (U.S. Patent No. 6,130,316; hereafter "Freeman"). Applicants traverse.

The standard required for finding anticipation under 35 U.S.C. § 102(e) is stated in MPEP § 2131 (emphasis added). "'A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference.' *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). 'The identical invention must be shown in

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as complete detail as is contained in the...claim.' *Richardson v. Suzuki Motor Co.* 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989)." Freeman fails to meet this standard, and thus does not anticipate the instant invention as claimed.

Claim 1 of the invention comprises a method for transplanting cells to a patient in need thereof, comprising obtaining cells from a donor, contacting the donor cells with an immunoglobulin specific to B7-1, an immunoglobulin specific for B7-2, and recipient cells from a patient from about 1 to about 48 hours, thereby obtaining a mixture, and introducing the mixture to the patient. Claims 2-4 are dependent on claim 1.

The Examiner alleges that Freeman teaches the use of B7-2 specific antibodies, including recombinant antibodies thereof, in order to cause immunosuppression or induce tolerance, including their use to inhibit transplant rejection in various modalities. The Examiner further alleges that Freeman teaches the use of inhibitory B7-2 specific antibodies in combination with other immunsuppressive reagents. However, Freeman does not teach a method for transplanting cells to a patient in need thereof, wherein donor and recipient cells from the patient are combined in mixture *ex vivo*, and wherein the mixture is introduced to the patient. Instead, in Freeman the antibodies are administered directly to the patient (see column 34, lines 47-54).

Accordingly, Applicants contend that Freeman does not rise to the level of being anticipatory of the instant claimed invention because Freeman does not teach each and every element of the claimed invention. Applicants request that the rejection under 35 U.S.C. § 102(e) be withdrawn.

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IV. The Rejection Under 35 U.S.C. § 102(b)

Claims 1-10 stand rejected under 35 U.S.C. §102(b) as allegedly anticipated by Blazar et al. (WO 95/34320; hereafter "Blazar"). Office Action at page 4. The standard required for finding anticipation under 35 U.S.C. § 102(b) is the same as noted above under 35 U.S.C. § 102(e), namely, a claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described in a single prior art reference. MPEP § 2131.

The Examiner alleges that Blazer teaches the use of inhibitors including those that bind both B7-1 and B7-2 to induce T cell unresponsiveness for bone marrow transplantation, including its use for the treatment of haematological malignancies and anemia. The Examiner also notes that Blazar teaches that the inhibitory agents can be administered for 18-36 hours after T cell priming.

A central limitation of the claimed invention comprises contacting the donor cells with an immunoglobulin specific to B7-1, an immunoglobulin specific to B7-2, and recipient cells from the patient for a period of time of from about 1 to about to 48 hours before being introduced to the patient. This element is not taught by Blazar. Instead, Blazar teaches that donor and recipient cells may be incubated with immunoglobulins for a period of 2.5 to 4 days (page 28, lines 20-32). Blazar's reference to 18-36 hours refers to another step in the process, T-cell priming, where donor and recipient cells are combined before the antibody is added. In contrast, the present invention teaches the

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incubation of donor and recipient cells with the antibody for from about 1 to about 48 hours prior to introduction to the patient.

Accordingly, Applicants contend Blazar does not rise to the level of being anticipatory of the instant claimed invention because Blazar does not teach each and every element of the claimed invention. Applicants request that the rejection under 35 U.S.C. § 102(b) be withdrawn.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants respectfully request the reconsideration and reexamination of this application and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this filing and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

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Dated: July 26, 2002

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APPENDIX OF AMENDMENTS

Paragraph at page 2, beginning at line 24:

The invention also embodies a humanized immunoglobulin having a binding specificity for B7-2 comprising a heavy chain and/or a light chain. The light chain comprises a CDR (e.g., CDRI, CDR2 and CDR3) derived from an antibody of nonhuman origin which binds B7-2 and a FR derived from a light chain of human origin (e.g., H2F antibody). The heavy chain comprises a CDR (e.g.,CDRI, CDR2 and CDR3) derived from an antibody of nonhuman origin which binds B7-2 and a FR region derived from a heavy chain of human origin (e.g., the human [I2R] III2R antibody). The immunoglobulin can further comprise CDR1, CDR2 and CDR3 for the light or heavy chain having the amino acid sequence set forth herein or an amino acid.

Paragraph at page 3, beginning at line 21:

Another embodiment of the invention is a humanized immunoglobulin heavy chain that is specific for B7-2 and comprises CDRI, CDR2 and/or CDR3 of the heavy chain of the 3D1 antibody, and a human heavy chain FR (e.g., [I2R] III2R antibody). The invention pertains to a humanized immunoglobulin heavy chain that comprises a variable region shown in Figure 2A (SEQ ID NO: 6). The invention also pertains to an isolated nucleic acid sequence that encodes a humanized variable heavy chain specific for B7-2 that comprises a nucleic acid, such as the sequence shown in Figure 2A (SEQ ID NO: 5), a nucleic acid that encodes the amino acid sequence shown in Figure 2A

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(SEQ ID NO: 6), a nucleic acid which hybridizes thereto under stringent hybridization conditions, and a nucleic acid which is the complement thereof.

Paragraph at page 35, beginning at line 1:

To retain the binding affinity of the mouse antibody in the humanized antibody, the general procedures of Queen *et al.* were followed (Queen *et al. Proc. Natl. Acad Sci. USA* 86: 10029 (1989), U.S. Patent Nos. 5,585,089 and 5,693,762, the teachings of which are incorporated herein in their entirety). The choice of framework residues can be critical in retaining high binding affinity. In principle, a framework sequence from any human antibody can serve as the template for CDR grafting; however, it has been demonstrated that straight CDR replacement into such a framework can lead to significant loss of binding affinity to the antigen (Tempest *et al.*, *Biotechnology* 9: 266 (1992); Shalaby *et al.*, *J. Exp. Med.* 17: 217 (1992)). The more homologous a human antibody is to the original murine antibody, the less likely the human framework will introduce distortions into the mouse CDRs that could reduce affinity. Based on a sequence homology, [I2R] III2R was selected to provide the framework for the humanized 3D1 heavy chain and H2F for the humanized 3D1 light chain variable region. Manheimer-Lory, A. *et al.*, *J. Exp. Med.* 174(6):1639-52 (1991). Other highly homologous human antibody chains would also be suitable to provide the humanized antibody framework, especially kappa light chains from human subgroup 4 and heavy chains from human subgroup 1 as defined by Kabat.

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Paragraph at page 35, beginning at line 18:

Normally the heavy chain and light chain from the same human antibody are chosen to provide the framework sequences, so as to reduce the possibility of incompatibility in the assembling of the two chains. The [I2R] III2R antibody shows a high homology to the 3D1 heavy and light chains and thus, was chosen to provide the framework for the initial humanized antibody model. The 3D1 light chain variable region, however, shows a significantly higher homology to the H2F framework compared to any others, including [I2R] III2R. Therefore, H2F was chosen instead to provide the framework for the humanized 3D1 light chain variable region, while [I2R] III2R was selected to provide the framework for the heavy chain variable region.

Paragraph at page 36, beginning at line 1:

The computer programs ABMOD and ENCODE (Levitt *et al.*, *J. Mol. Biol.* 168: 595 (1983)) were used to construct a molecular model of the 3D1 variable domain, which was used to locate the amino acids in the 3D1 framework that are close enough to the CDRs to potentially interact with them. To design the humanized 3D1 heavy and light chain variable regions, the CDRs from the mouse 3D1 heavy chain were grafted into the framework regions of the human [I2R] III2R heavy chain and the CDRs from the mouse 3D1 light chain grafted into the framework regions of the human H2F light chain. At framework positions where the computer model suggested significant contact with the CDRs, the amino acids from the mouse antibody were substituted for the original human framework amino acids. For humanized 3D1, this was done at residues 27, 30,

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48, 67, 68, 70 and 72 of the heavy chain and at residue 22 of the light chain. Furthermore, framework residues that occurred only rarely at their positions in the database of human antibodies were replaced by a human consensus amino acid at those positions. For humanized 3D1 this was done at residue 113 of the heavy chain and at residue 3 of the light chain.

Paragraph at page 37, beginning at line 12:

Likewise, many of the framework residues not in contact with the CDRs in the humanized 3D1 heavy and light chains can accommodate substitutions of amino acids from the corresponding positions of [I2R] III2R and H2F frameworks, from other human antibodies, from the mouse 3D1 antibody, or from other mouse antibodies, without significant loss of the affinity or non-immunogenicity of the humanized antibody. Table 2 lists a number of additional positions in the framework where alternative amino acids may be suitable.

1. (Amended) A method for transplanting cells to a patient in need thereof, comprising:

a) obtaining cells from a donor,

b) obtaining recipient cells from the patient,

c) contacting the donor cells with an immunoglobulin specific to B7-1, an immunoglobulin specific to B7-2, and recipient cells from the patient for a period of time [sufficient for tolerance induction] from about 1 to about 48 hours, thereby obtaining a

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mixture, and

[c)] d) introducing the mixture to the patient.

9. (Amended) A method for transplanting cells to a patient in need thereof, comprising:

a) obtaining cells from a donor,

b) obtaining a tissue, an organ, or recipient cells from the patient,

c) contacting the donor cells with an immunoglobulin specific to B7-1, an immunoglobulin specific to B7-2, and the tissue, the organ, or the recipient cells that express MHC Class I antigen, B7-1 and B7-2 molecules, for a period of time [sufficient for tolerance induction] from about 1 to about 48 hours, thereby obtaining a mixture, and

[c)] d) introducing the mixture to the patient.

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